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(54) Title: DIHYDROPYRIMIDO-QUINOXALINES AND DIHYDROPYRIMIDO-PYRIDOPYRAZINES USEFUL FOR TREATING TUMOURS

(57) Abstract

Dihydropyrimido-quinoxalines and dihydropyrimido-pyridopyrazines are useful in the treatment of cancer and in particular the treatment of hypoxic tumours.

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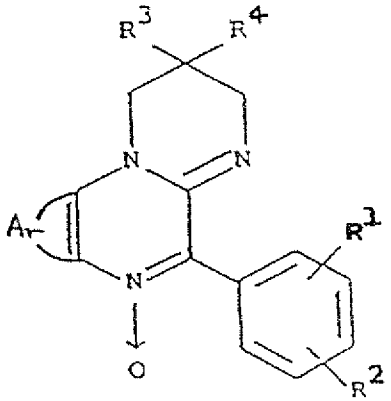
DIHYDROPYRIMIDO-QUINOXALINES AND DIHYDROPYRIMIDO-PYRIDOPYRAZINES USEFUL FOR TREATING TUMOURS

The present invention relates to the use of dihydropyrimido-quinoxalines and dihydropyrimido-pyridopyrazines in the manufacture of medicaments useful in the treatment of cancer.

EP-A-256,545 and EP-A-257,508 disclose quinoxaline and pyridopyrazine derivatives which are useful as anti-anaerobic agents, for the treatment of diseases related to anaerobic bacteria. Such diseases include for example, post-operative sepsis following lower gastrointestinal surgery or female urinogenital surgery, pelvic inflammatory disease, ulcers, gangrene, trichomonal vaginitis, non-specific vaginitis, amoerbiasis, giardiasis, periodontal disease, acne, and the like.

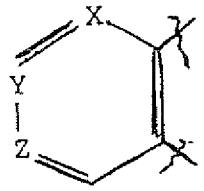
Accordingly the present invention provides the use in the manufacture of a medicament, for use the treatment of a tumour, such as a hypoxic tumour, of a compound of formula (I)



(I)

in which

Ar forms, together with the carbon atoms to which is attached, a fused benzene ring optionally substituted by halogen (i.e. fluorine, chlorine, bromine or iodine) or trifluoromethyl or a group of formula (II)

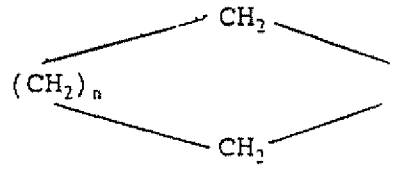


(II)

where one of X, Y and Z is -N= and the other two are -CH=,

R^1 and R^2 are the same or different and each is hydrogen, halogen, i.e. fluorine, chlorine, bromine or iodine, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms; and

R^3 and R^4 are the same or different and each is alkyl of 1 to 6 carbon atoms or together R^3 and R^4 form a group:



where n is from 0 to 4; and

and pharmaceutically acceptable salts thereof.

According to a further feature the present invention provides a method for the treatment of a human or animal patient suffering from a tumour, such as a hypoxic tumour, which method comprises administering to the patient an effective amount of a compound of Formula (I), as

hereinbefore defined, or a pharmaceutically acceptable salt thereof.

The invention provides, as a further feature, products comprising a compound of Formula (I) as hereinbefore defined or a pharmaceutically acceptable salt thereof, for use in the treatment of a tumour, such as a hypoxic tumour.

The invention provides, as yet a further feature, a pharmaceutical agent for use in the treatment of a tumour, such as a hypoxic tumour, which agent comprises a compound of Formula (I) as hereinbefore defined, or a pharmaceutically acceptable salt thereof.

In the compounds of formula (I), the alkyl and alkoxy groups may be either straight or branched.

It is preferred that any alkyl groups in the compounds of formula (I) (including alkyl groups which form part of alkoxy groups) be alkyl groups of 1 to 4 carbon atoms, ie methyl, ethyl, n-propyl, isopropyl, n-butyl, secbutyl or tert-butyl.

The most preferred alkyl substituents are methyl and ethyl.

In the compounds of formula (I) the phenyl ring bearing the groups R^1 and R^2 may be substituted in any position by 1 or 2 substituents selected from halogen atoms e.g. bromine, chlorine or fluorine atoms, and alkyl, e.g. methyl, and alkoxy, e.g. methoxy, groups. The following substituted

phenyl groups are illustrative of such groups: 4-chlorophenyl, 4-fluorophenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 3-bromophenyl, 3-chlorophenyl, 2-methoxyphenyl, 4-methoxypenyl, 3-methoxyphenyl, 2-ethoxyphenyl, 3-ethoxyphenyl, 4-ethoxyphenyl, 3,4-dimethoxyphenyl, 3,5-dimethoxyphenyl, 3,4-diethoxyphenyl, 3,5-diethoxyphenyl, 2-chloro-4-methoxyphenyl, 4-methylphenyl and 2,4-dimethylphenyl.

Preferred compounds of formula (I) are those in which R^1 and R^2 are both hydrogen i.e. the phenyl ring bearing R^1 and R^2 is unsubstituted.

Also preferred are compounds of formula (I) in which R^3 and R^4 are methyl or ethyl, and more preferably R^3 and R^4 are both methyl or both ethyl. Most preferably R^3 and R^4 are both methyl.

Preferably Ar is a group of formula (II). More preferably X is -CH= and one of Y and Z is -N= and the other -CH=. Still more preferably, X and Z are -CH= and Y is -N=.

Of the compounds of formula (I) 2,3-dihydro-2,2-dimethyl-5-phenyl-1H-pyrimido[1,2-a]pyrido[3,4-e]pyrazine-6-oxide and 2,3-dihydro-2,2-diethyl-5-phenyl-1H-pyrimido[1,2-a]pyrido [3,4e]pyrazine-6-oxide may be specifically mentioned as particularly preferred. Of these two the dimethyl compound is more preferable.

Salts of the compounds of formula (I) used in the

present invention may be any pharmaceutically acceptable acid addition salts. Examples of suitable salts include, salts of inorganic acids such as chlorides, bromides, iodides, phosphates and sulphates and salts of organic acids such as acetates, citrates, lactates and tartrates.

The compounds of Formula (I) may, according to the invention, be used in uncomplexed form or in the form of a complex such as a complex formed with one or more molecules of organic solvent, water (i.e. a hydrate) or hydrogen halide, e.g. hydrogen chloride.

The compounds used in the present invention are known compounds which may be prepared using known methods. In particular they may be prepared according to procedures described in EP-A-256,545 and EP-A-257,508.

The compounds of formula (I) are useful in increasing the sensitivity of tumour cells to radiation in radiotherapy and as bioreductive agents. A compound is administered to a patient having a radiation-treatable cancer, prior to or after, more typically shortly after irradiation of the tumour, in an amount effective to increase the sensitivity of the tumour cells to the effects of the irradiation.

Any solid tumour, which may have regions where cells are radiobiologically hypoxic and become resistant to ionising radiation, may be treated. Examples of such tumours are epithelial tumours of the head, neck, thorax and abdomen, soft tissue sarcomas and brain tumours. The compounds of

formula (I) can therefore be employed in the radiotherapy of all such solid tumours where hypoxic cells are known or suspected to exist.

The compounds of formula (I) may also be used where an agent having differential hypoxic cytotoxicity is required. The compounds can be employed for chemopotentiation of a chemotherapeutic agent or as a chemotherapeutic by administration of a compound (I) to a patient having a localised or metastatic cancer. Administration is carried out prior to simultaneously with or after administration, typically prior to or simultaneously with, of a chemotherapeutic agent such as melphalan, cyclophosphamide, 5-fluorouracil, adriamycin, CCNU(1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) or tumour necrosis factor (TNF). Any solid tumours, such as above, which are primary or secondary deposits, where it is known or suspected that hypoxic cells are present can therefore benefit from treatment employing a compound of formula (I).

The compounds of formula (I) are useful in particular for the treatment of hypoxic tumours. However the compounds of formula (I) may also be useful in the treatment of other tumours rich in enzymes required to activate the compounds of formula (I) as bioreductive agents or radiosensitisers. Such enzymes may include cytochrome P450, NADPH dependent cytochrome p450 reductase, DT-diaphorase and xanthine oxidase.

The compounds of formula (I) and salts thereof may be administered orally or intravenously. The amount administered depends on factors such as the cancer, the condition of the patient and the body weight of the patient. Typically, however, doses of 50 to 1000 mg/m^2, of a patient's body area may be employed.

A compound of formula (I) may be formulated in a manner appropriate to the treatment for which it is to be used by bringing it into association with a pharmaceutically compatible carrier or diluent. The compound may be included in a dosage form suitable for bolus injection or such as a tablet or capsule, for example a capsule comprising known formulation components. The compound may also be formulated for intravenous administration e.g. in a saline drip solution.

The following Example illustrates the invention.

EXAMPLE 1

The toxicity of RB 90008X [2,3-dihydro-2,2-diethyl-5-phenyl-1H-pyrimido [1,2-a]pyrido [3,4-e] pyrazine-6-oxide] towards aerobic or hypoxic V79 cells in vitro is shown in Table 2 and comparison is made with SR 4233 [3-amino-1,2,4-benzotriazine 1,4-dioxide. Toxicity was determined by the use of the modified MTT assay (Stratford and Stephens (1989), Int. J. Radiat. Oncol. Biol. Phys. 16, 973-976). Values

quoted represent concentrations of drug required to reduce proliferation of treated cultures by 50%. Cells are treated with various drug doses for 3 hours at 37°C under aerobic or hypoxic conditions, following drug removal cells are allowed to proliferate for 3 days prior to assay.

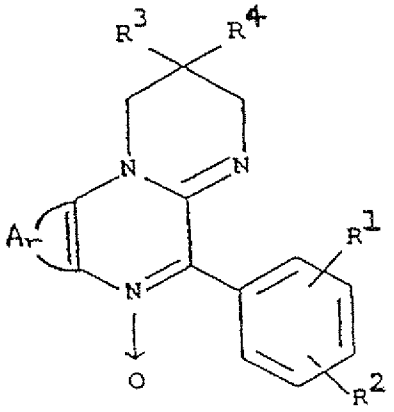
TABLE 2

Compound	C air	C N_2	Ratio
	mmol dm^{-3}		
RB 90008X	3.0	0.3	10
SR 4233	0.3	0.006	50

Clearly RB90008X is substantially more toxic to hypoxic compared with aerobic cells. While the differential is higher for SR 4233, the aerobic toxicity of the mono-N-oxide is considerably less.

CLAIMS

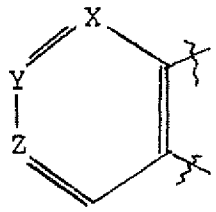
1. Use in the manufacture of a medicament, for use in the treatment of a tumour, of a compound of formula (I)



(I)

in which

Ar forms, together with the carbon atoms to which is attached, a fused benzene ring optionally substituted by halogen or trifluoromethyl or a group of formula (II)

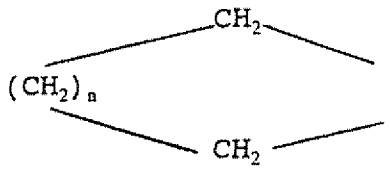


(II)

where one of X, Y and Z is -N= and the other two are -CH=,

R^1 and R^2 are the same or different and each is hydrogen, halogen, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms; and

R^3 and R^4 are the same or different and each is alkyl of 1 to 6 carbon atoms or together R^3 and R^4 form a group:



where n is from 0 to 4;

or a pharmaceutically acceptable salt thereof.

2. Use according to claim 1 of a compound of formula (I) in which R^1 and R^2 are both hydrogen, or a pharmaceutically acceptable salt thereof.

3. Use according to claim 1 or 2 of a compound of formula (I) in which R^3 and R^4 are the same or different and each is methyl or ethyl, or a pharmaceutically acceptable salt thereof.

4. Use according to claim 3 of a compound of formula (I) in which R^3 and R^4 are both methyl or both ethyl or a pharmaceutically acceptable salt thereof.

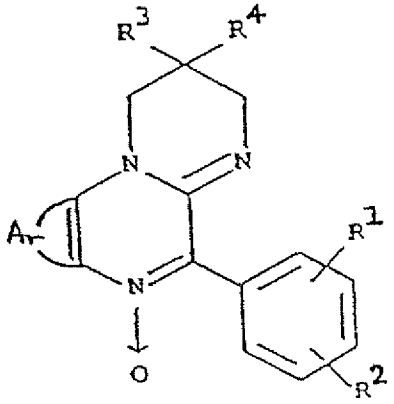
5. Use according to any one of claims 1 to 4 of a compound of formula (I) in which Ar is a group of formula (II) in which X and Z are -CH= and Y is -N= or a pharmaceutically acceptable salt thereof.

6. Use according to claim 1 of a compound of formula (I) which is 2,3-dihydro-2,2-dimethyl-5-phenyl-1H-pyrimido[1,2-a]pyrido[3,4-e]pyrazine-6-oxide or 2,3-dihydro-2,2-diethyl-5-phenyl-1H-pyrimido[1,2-a]pyrido[3,4e]pyrazine-6-oxide or a pharmaceutically acceptable salt thereof.

7. Use according to claim 6 of a compound of formula (I) which is 2,3-dihydro-2,2-dimethyl-5-phenyl-1H-pyrimido[1,2-a]pyrido[3,4e]pyrazine-6-oxide or a pharmaceutically acceptable salt thereof.

8. Use according to any one of the preceding claims, for use in the treatment of a hypoxic tumour.

9. A method for the treatment of a human or animal patient suffering from a tumour which method comprises administering to the patient an effective amount of a compound of Formula (I)



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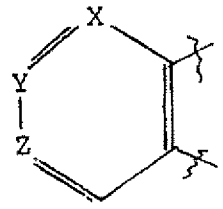

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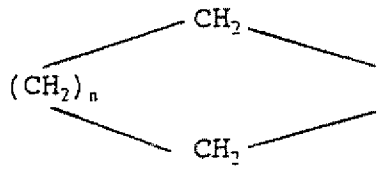
where one of X, Y and Z is -N= and the other two are -CH=,

R^1 and R^2 are the same or different and each is hydrogen, halogen, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms; and

R^3 and R^4 are the same or different and each is alkyl of 1 to 6 carbon atoms or together R^3 and R^4 form a group:



where n is from 0 to 4;

or a pharmaceutically acceptable salt thereof.

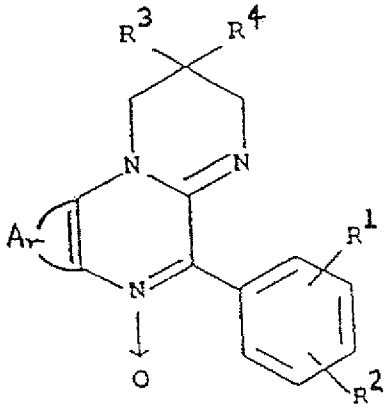
10. A method according to claim 9 for the treatment of a patient having a solid tumour in which it is known or suspected that hypoxic cells are present.

11. A method according to claim 9 or 10, in which the tumour is a radiation-treatable cancer, the compound of formula (I) or salt thereof is administered to increase the sensitivity of the tumour to the effects of irradiation, and the tumour is then irradiated, the compound of formula (I) being administered prior to or after irradiation of the tumour.

12. A method according to claim 9 or 10, in which the compound of formula (I) or salt thereof is administered for chemopotentiation of a chemotherapeutic agent and the chemotherapeutic agent is administered prior to, after or

simultaneously with the compound of formula (I) or salt thereof.

13. Products for use in the treatment of a tumour, comprising a compound of formula (I)



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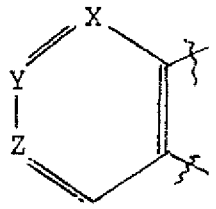

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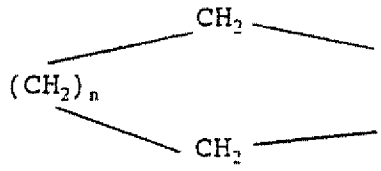
where one of X, Y and Z is -N= and the other two are -CH=,

R^1 and R^2 are the same or different and each is hydrogen, halogen, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms; and

R^3 and R^4 are the same or different and each is alkyl of 1 to 6 carbon atoms or together R^3 and R^4 form a group:

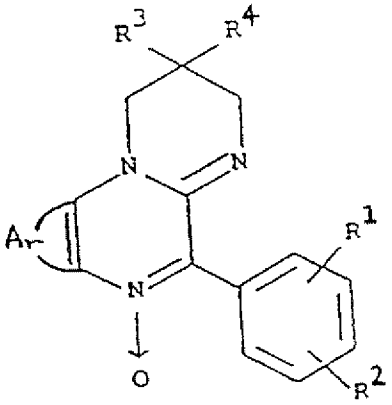


where n is from 0 to 4;

or a pharmaceutically acceptable salt thereof.

14. Products according to claim 13 for use in the treatment of a hypoxic tumour.

15. A pharmaceutical agent for use in the treatment of a tumour, which agent comprises a compound of Formula (I)



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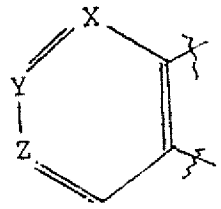

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where one of X, Y and Z is -N= and the other two are -CH=,

R^1 and R^2 are the same or different and each is hydrogen, halogen, alkyl of 1 to 6 carbon atoms or alkoxy of 1 to 6 carbon atoms; and

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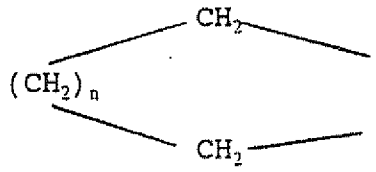

where n is from 0 to 4;

or a pharmaceutically acceptable salt thereof.

16. An agent according to claim 15 for use in the treatment of a hypoxic tumour.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 31/505

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	EP,A,0256545 (G.D. SEARLE & CO.) 24 February 1988, see whole document (cited in the application)	1-12
X		13-16
A	EP,A,0257508 (G.D. SEARLE & CO.) 2 March 1988, see abstract; examples; claims (cited in the application)	1-12
X		13-16

-/-

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
04-09-1992	30. 10. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE ...

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	Chemical Abstracts, vol. 101, no. 7, 13 August 1984, (Columbus, Ohio, US), P.C. PARTHASARATHY et al.: "Heterocycle N-oxides: Part II - Syntheses of new ring systems N-oxides of dihydroimidazo- and pyrimido[2,1-h]pteridines and azadihydroimidazo- and pyrimido[1,2-a]quinoxalines and their antiprotozoal activities", see page 618, abstract no. 55037b, & INDIAN J. CHEM., SECT. B 1983, 22B(12), 1233-5, see abstract	1-16
A	Chemical Abstracts, vol. 101, no. 7, 13 August 1984, (Columbus, Ohio, US), P.C. PARTHASARATHY et al.: "Heterocyclic N-oxides: Part I - Syntheses of 1,2-dihydroimidazo[1,2-a]quinoxaline 5-oxides and 2,3-dihydro-1H-pyrimido[1,2-a]quinoxaline 6-oxides and their antiprotozoal activity", see page 618, abstract no. 55038c, & INDIAN J. CHEM., SECT. B 1983, 22B(12), 1250-1, see abstract	1-16
A	WO,A,9007496 (SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH) 12 July 1990, see abstract; page 1, line 10 - page 2, line 25; claims 1-5	1-16
A	Journal of Organic Chemistry, vol. 43, no. 10, 1978, American Chemical Society, M.J. STRAUSS et al.: "Annelations of amidines in halonitroaromatics. A one-step route to quinoxaline and imidazoquinoxaline N-oxides and related structures", pages 2041-2044, see whole document	1-16

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

ALTHOUGH CLAIMS 9-12 ARE DIRECTED TO A METHOD OF TREATMENT OF THE HUMAN/ANIMAL BODY THE SEARCH HAS BEEN CARRIED OUT AND BASED ON THE ALLEGED EFFECTS OF THE COMPOUND/COMPOSITION.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. GB 9201204
SA 61620

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 07/10/92
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